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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/043,658	01/09/2002	Eric N. Olson	MYOG:024USC1	7444

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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/043,658	OLSON, ERIC	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4 and 9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a continuation of 09/438,075, filed November 10, 1999, now US Patent 6,372,957, which claims benefit to provisional applications 60/107,755, filed November 10, 1998 and 60/108,083, filed November 12, 1998.

Applicant's amendment filed October 4, 2004, has been received and entered. The specification has been amended. Claims 2, 3, 5-8 and 10-31 have been canceled. Claims 1, 4 and 9 are pending.

Election/Restrictions

Applicant's election without traverse of group III, claims 4 and 9, in the reply filed on April 5, 2004, was acknowledged.

As noted previously, claim 1 link(s) inventions I-III. Claim 1 has not been amended and still encompasses any form of inhibiting MEF2 to treat hypertrophy. Elected group III, claims 1, 4 and 9, drawn to a method of treating hypertrophy in a cardiomyoctye comprising the steps of (1) decreasing the expression of MEF2 gene; and (2) further decreasing the expression of a gene that is upregulated by MEF2, are currently under examination.

The restriction requirement between the linked inventions is subject to the nonallowance of the linking claim(s), claim 1. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to

examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP ' 804.01.

Response to Amendment

It is noted in Applicant's arguments mention is made of an affidavit from Dr. McKinsey has been filed. See page 7, bottom of first full paragraph of Applicants amendment. However, upon review of the file it appears that a declaration has not been received by the office, and review of the transmittal letter with the instant amendment does not indicate that one was filed.

Information Disclosure Statement

It is noted in Applicant's arguments mention is made of references that were provided to support arguments made in the amendment. However, upon review of the file it appears that neither an IDS, nor references have received by the office. Further, a review of the transmittal letter with the instant amendment does not indicate that the material was filed.

An attempt to obtain the references based on the cited author and year published has been made by the Examiner. What appears to be the relevant references have been made of record.

Specification

The nucleotide sequence disclosure contained in this application complies with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825.

The filing of a sequence listing and the amendments to the specification have addressed the requirements of 37 CFR 1.821-1.825.

Claim Objections

Claim 1 is objected to because of the following informalities:

Applicants have elected Group III, drawn to a method of treating hypertrophy in a cardiomyoctye comprising the steps of (1) decreasing the expression of MEF2 gene; and (2) further decreasing the expression of a gene that is upregulated by MEF2. Claim 1 is broader than the elected invention. It is noted that claim 1 is a linking claim, however this claim and subject matter has not been found allowable. Accordingly, the scope of the claim should be amended to reflect the elected invention.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4 and 9 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant argues that while "[I]t may be true that inhibiting MEF2 to treat hypertrophy was not well known at the time the present application was filed" the instant specification coupled with what was known in the prior art would allow one of skill in the art to practice the claimed invention, and that recent results validate the paradigm on which the instant invention is based (page 4). Applicant argues that the office is requiring experimental evidence confirming that each aspect of the claimed invention works (page 5). Applicant summarizes the information disclosed in the instant specification, citing supporting post filing art for the importance of MEF2 and class II HDACs interaction (page 6).

Applicants point to the specification for teachings of materials and ways to inhibit MEF2, and argue that it would not be undue experimentation to practice the method as claimed (pages 6-7). Citing the findings of *In re Robins*, Applicant argues that 35 USC 112 first paragraph requires that a "specification which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement . . . unless there is reason to doubt the objective truth of the statements therein." The Robins court also demands that "Section 112 requires nothing more than objective enablement. How such teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance." While more enablement may be required where the art is unpredictable, there is no *per se* rule for a working model. The invention must simply enable one of skill in the art to practice that invention, and there is nothing contained in the current

application that goes beyond the capabilities of one of skill in the art (page 7). See Applicants amendment, pages 4-7, Section II. Applicant's arguments have been fully considered, but not found persuasive.

The case law cited by Applicant is on point with the fact pattern of the instant application. However, unlike the simple chemical compounds reviewed in Robins, the instant invention encompasses methodology in a developing unpredictable art. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). As noted in the findings of the Robins court, in a unpredictable area of science an enabling disclosure commensurate in scope of the claimed invention is required (*In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). With respect to accepting the teachings of the specification as an enabling disclosure, Examiner has provided a *prima facie* case examining all the evidence of record regarding the scientific basis of the invention and the breadth of the claims, and has even cited post-filing references by the inventor acknowledging that even as of 2004 the inventor acknowledges that it is still to be determined whether MEF2 is involved in the pathogenic mechanisms associated with endothelial disorders (third column, page 1111, Olson JCI 113:1110-1112, 2004, and also see previous office action). In this case, the evidence provided in the instant specification and in the art of record supports a finding to doubt the instant specification provides the necessary guidance that enables the method as broadly claimed. The cited post filing references of Zhang *et al.* (2002) and McKinsey *et al.* (2002) seem to support the position of the office in that while MEF may be affected in hypertrophy response, the genes/proteins important in modulating the response are the class II HDACs. Examiner does not refute the evidence that MEF2 and HDAC may interact or that MEF interacts with other proteins,

rather the issue is specifically will inhibiting MEF2 result in any form of treatment of hypertrophy in a cardiomyocyte cell, and does the present specification provide adequate disclosure and guidance to affect the great breadth of the claim for the use of any means of inhibition. The conclusions of Zhang *et al.* (2002) clearly indicate the complexity of hypertrophy in the heart, and more specifically in the pathways that regulate the stress response (page 487, first column). Even with their experimental evidence Zhang *et al.* conclude that HDACs, not MEF2, "represent *potential* therapeutic targets" (*emphasis added*, page 487, first column). Similarly, McKinsey *et al.* provide evidence and conclude an importance of chromatin modifying enzymes in general, such as HDACs, for affecting muscle. The elected invention encompasses a method of treating hypertrophy in a cardiomyoctye comprising the steps of first decreasing the expression of MEF2 gene and further decreasing the expression of a gene that is upregulated by MEF2. From the evidence of record, since multiple pathways exist that end in a hypertrophic state lacking any clear and distinct role for MEF2 in all these pathways (Olson JCI 113:1110-1112, 2004) one would conclude that simply inhibiting MEF2 will have no affect.

Examiner has not required "experimental evidence confirming that each aspect of the claimed methods works" (page 5), and notes that working examples are not even a requirement of an enabling disclosure. However, 35 USC 112, first paragraph, requires that a disclosure enable a claimed invention. In this case, the evidence in the present specification fails to provide the necessary guidance to practice the method as broadly claimed. Moreover, post-filing art clearly indicates that while MEF2 expression is affected during muscle hypertrophy, other molecules that interact can interact with MEF2, other molecules *i.e.* HDACs, have proven to be the critical proteins that influence hypertrophy. This is consistent with the fact that MEF2 alone

does not regulate gene expression as acknowledged by the instant specification (page 5, top of page).

The general teachings in the present specification for practicing a variety of methods is noted, however, the instantly claimed method requires further inhibiting genes upregulated by MEF2. In this case, the instant specification does not identify any of these additional potential target genes required to practice the invention. While Examiner would acknowledge that the art teaches that family of MEF2 transcriptional factors regulate the expression of numerous muscle specific and growth factor inducible genes (for example Black *et al.* Ann Rev Cell Dev Bol 14:167-196), neither the art of record nor the instant specification teach which of these should even begin to target to affect hypertrophy. The instantly claimed method is based in part on the up-regulation of the MEF2 during hypertrophy and the important role of MEF2C in heart growth and development, however, the instant disclosure fails to provide a clear correlation that decreasing any MEF2 family member will affect hypertrophy and fails to provide any specific guidance to what further genes to target for inhibition.

35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). Further, it is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). In the

instant case, there is evidence that MEF2C plays a role in the signal transduction pathway that is activated during conditions that cause hypertrophy, however there is no nexus between this observation and the direct role of all the family members of MEF2 causing hypertrophy. While the evidence of record supports a role for MEF2 in signal transduction during hypertrophy the specification provides insufficient teaching and guidance that the therapeutic methods of treatment proposed would work, and would require undue experimentation to develop a method of treatment as required by the instant claims.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed. Therefore, for the reasons above and of record, the rejection is maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach